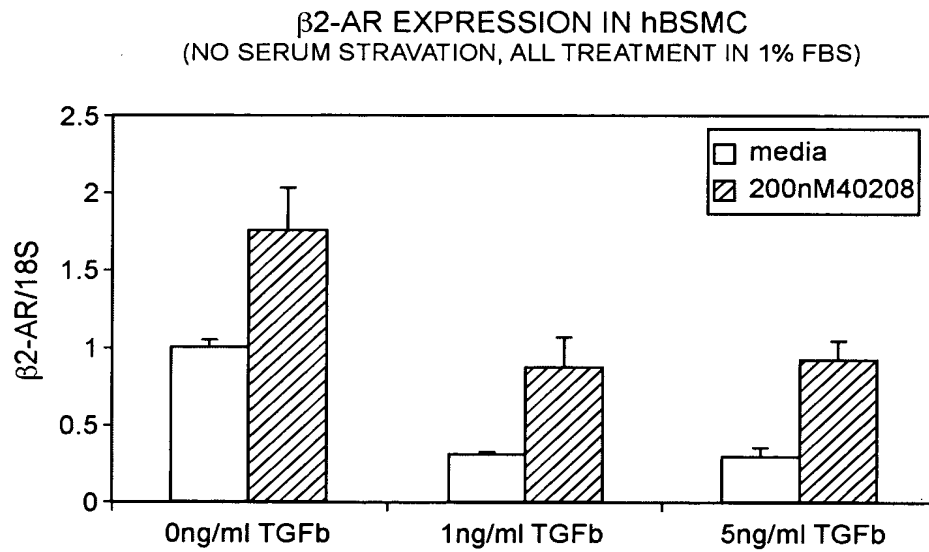


FIG. 1

TGF- β 1 EXPOSURE REDUCES β 2-AR mRNA
IN HUMAN BRONCHIAL SMOOTH MUSCLE CELLS

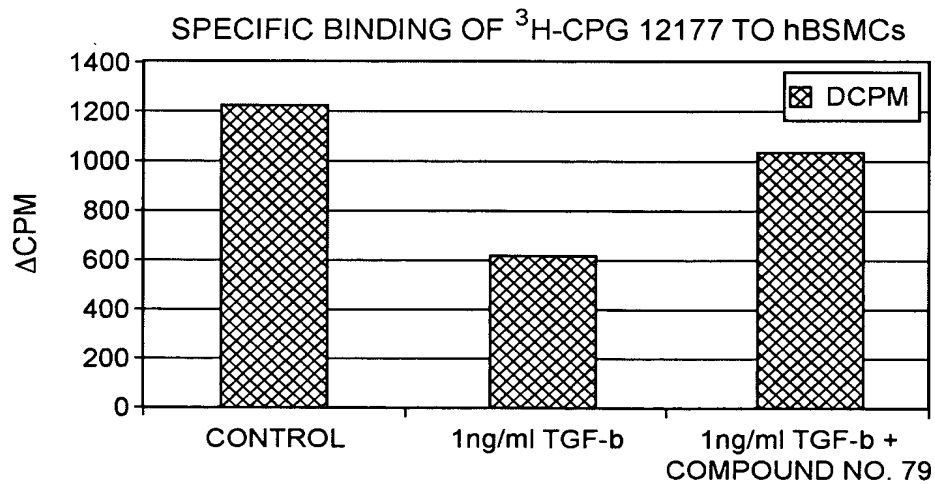
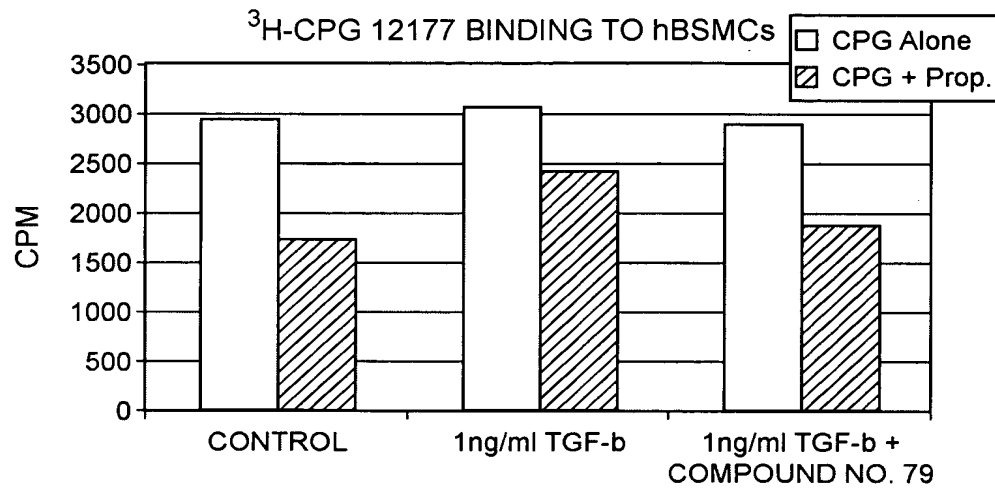


* β 1-AR mRNA IS UNDETECTABLE IN hBSMC

2/28

FIG. 2

TGF β EXPOSURE REDUCES β AR BINDING SITES ON hBSMC



3/28

FIG. 3

TGF β INDUCES Smad2 PHOSPHORYLATION AND REGULATES β 2-AR/AC SIGNALING IN hBSMC

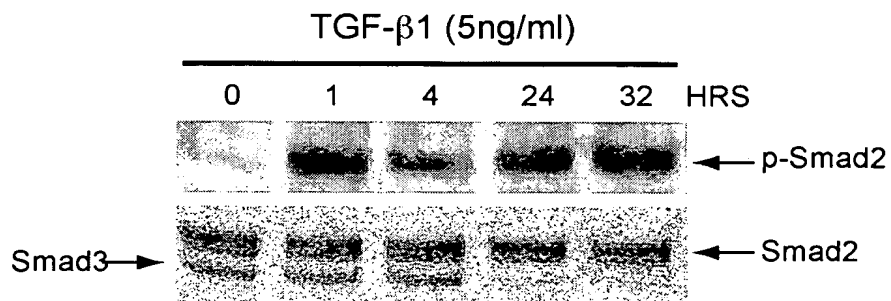
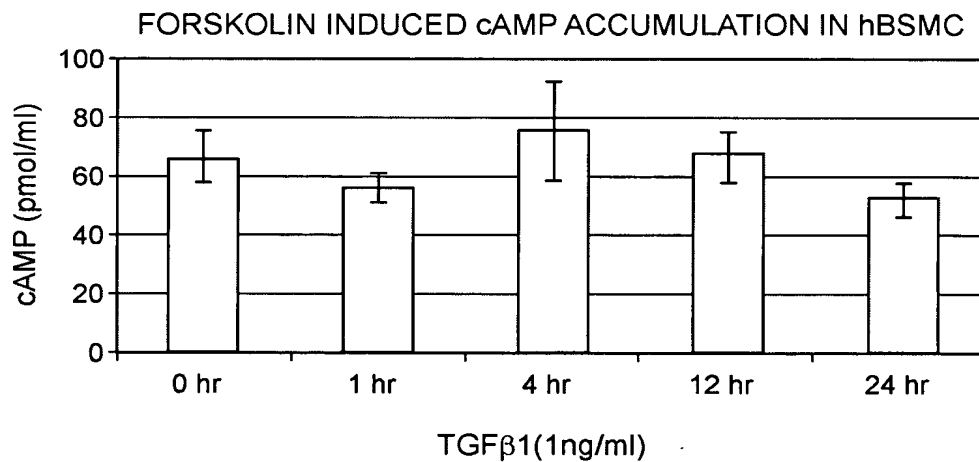
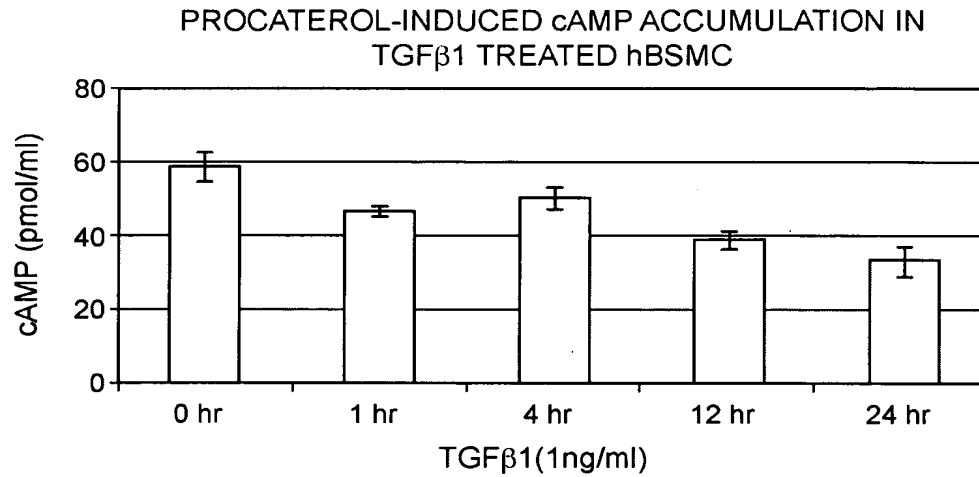
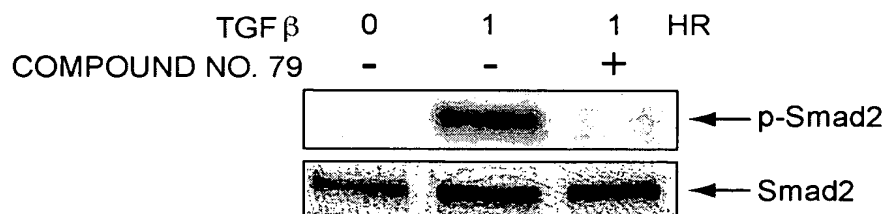
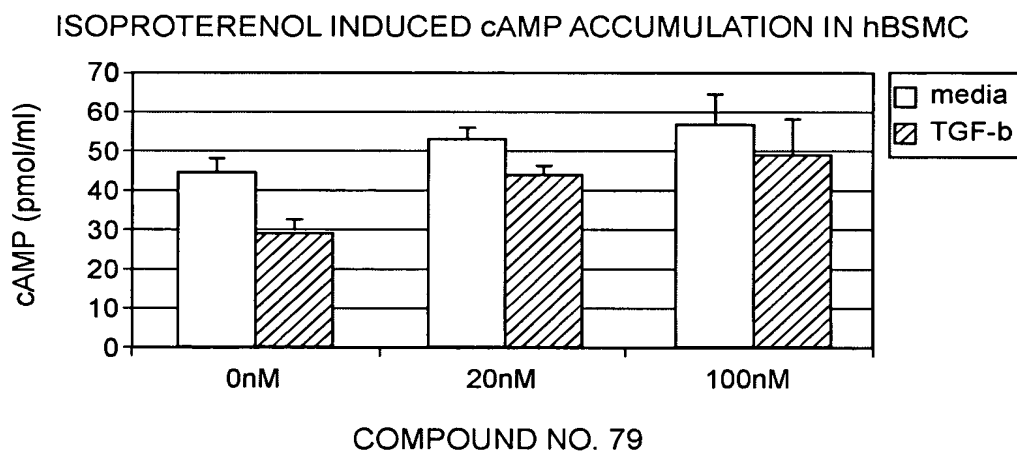
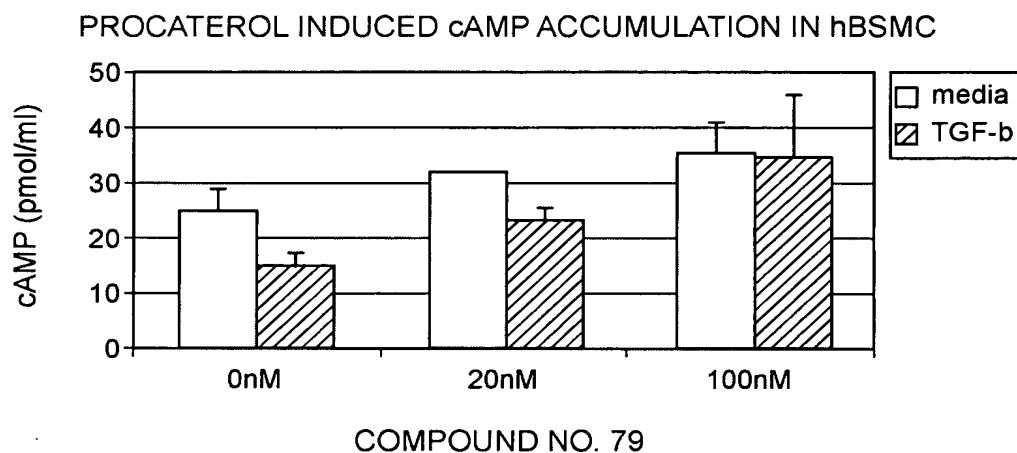


FIG. 4

TGF β -RI KINASE INHIBITORS PREVENT TGF β INDUCED LOSS OF ADRENERGIC RESPONSIVENESS IN hBSMC

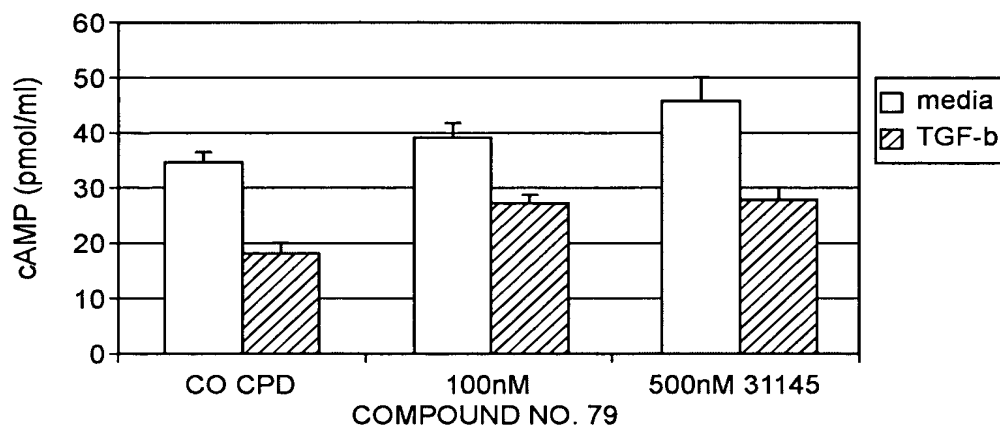


5/28

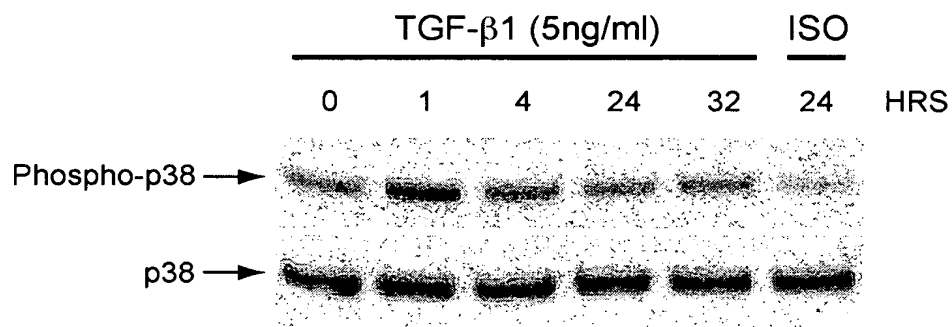
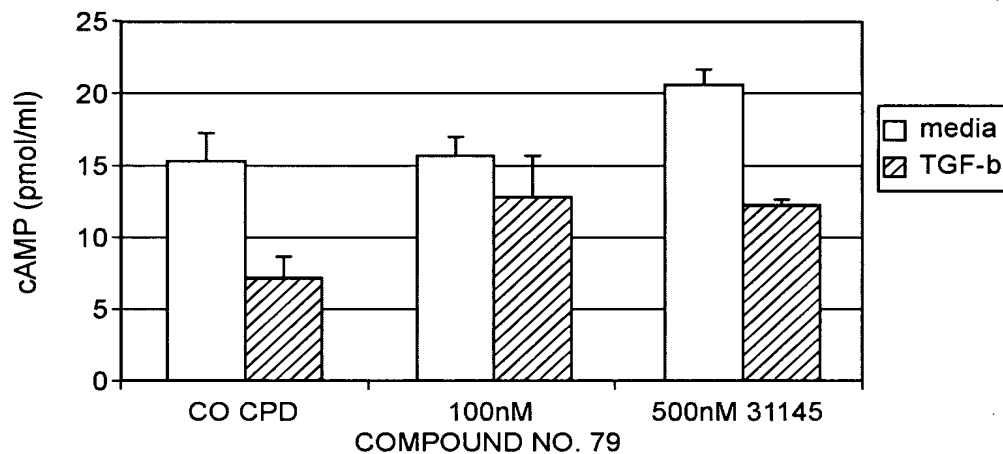
FIG. 5

IS p38 KINASE ALSO INVOLVED IN TGF β REGULATED
 β -AR SIGNALING IN hBSMC?

PROCATEROL INDUCED cAMP ACCUMULATION IN hBSMC



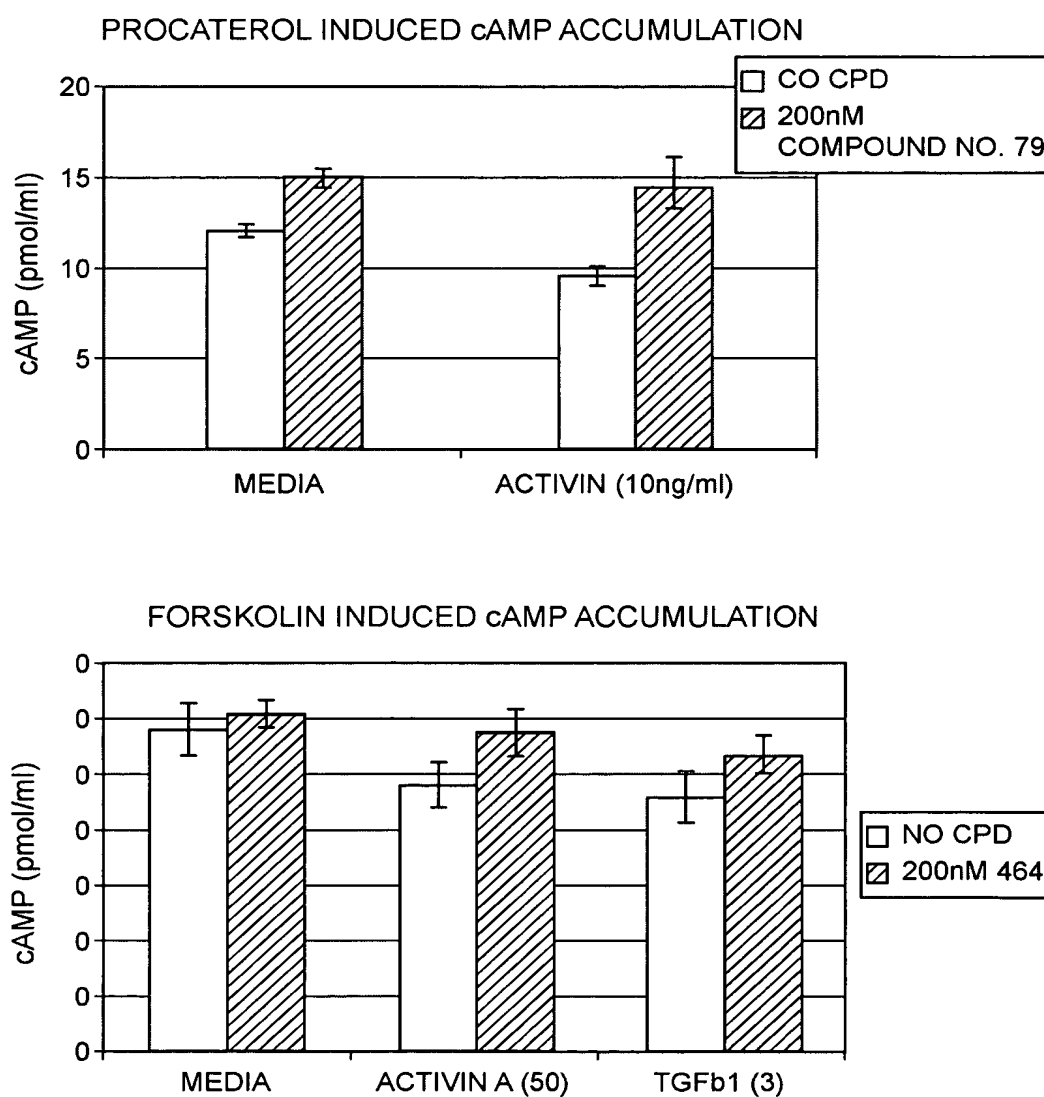
ALBUTEROL INDUCED cAMP ACCUMULATION IN hBSMC



6/28

FIG. 6

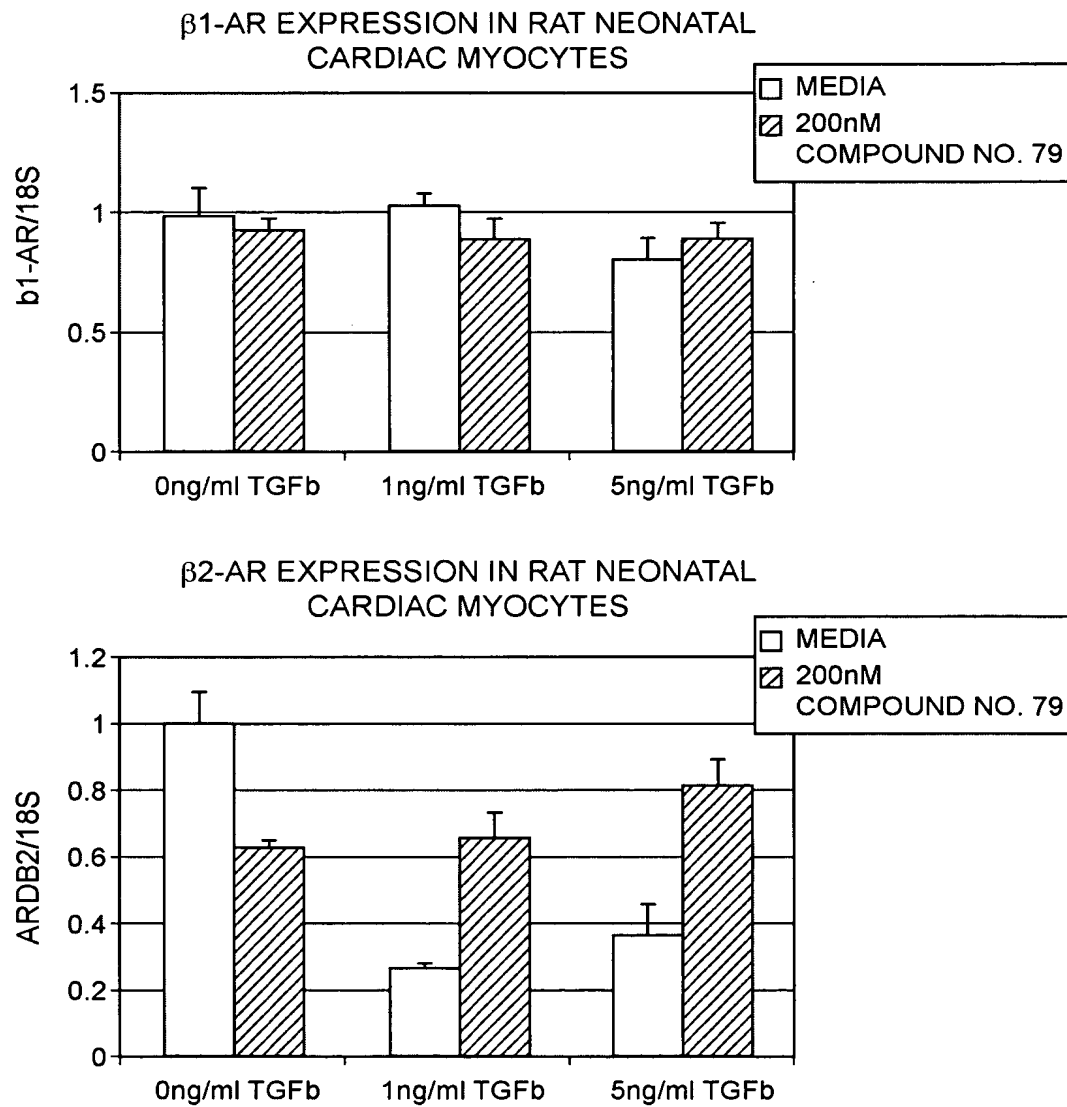
ACTIVIN INDUCED LOSS OF β AR RESPONSE/AC SIGNALING
IS ALSO REVERSED BY TGF β RI INHIBITOR IN hBSMC



7/28

FIG. 7

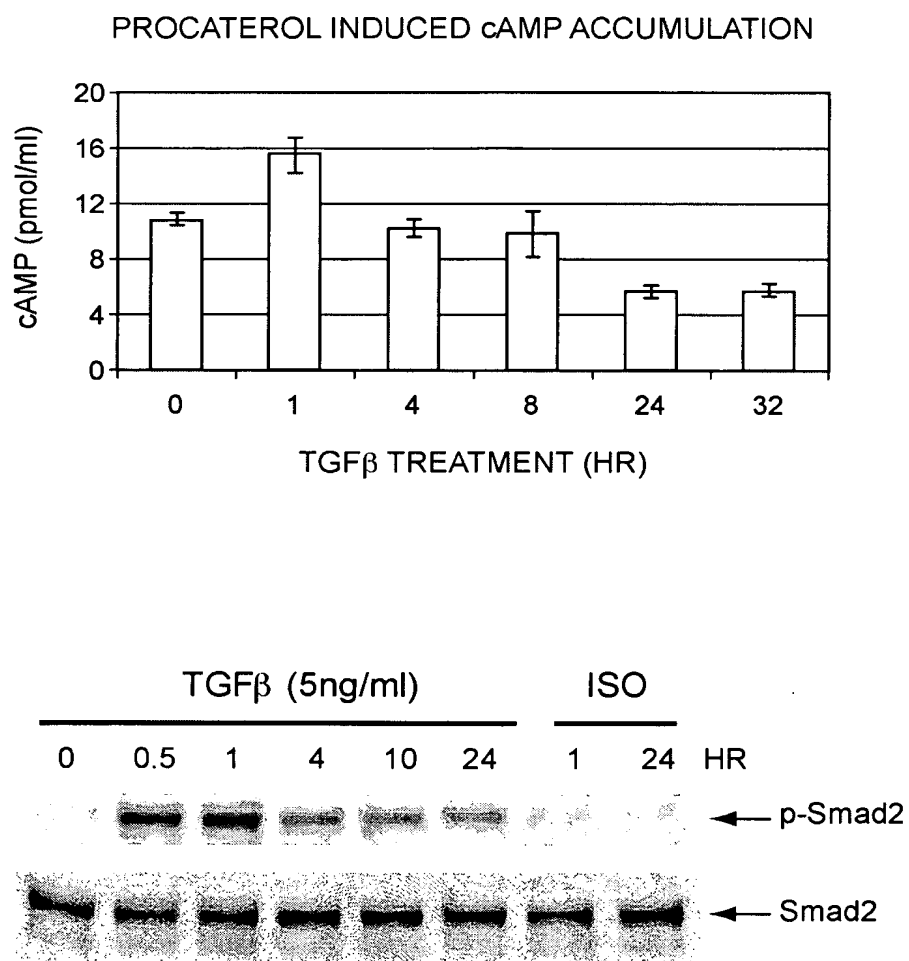
TGF β DOWN-REGULATES β 2-AR mRNA IN RAT NEONATAL CARDIOMYOCYTES



8/28

FIG. 8

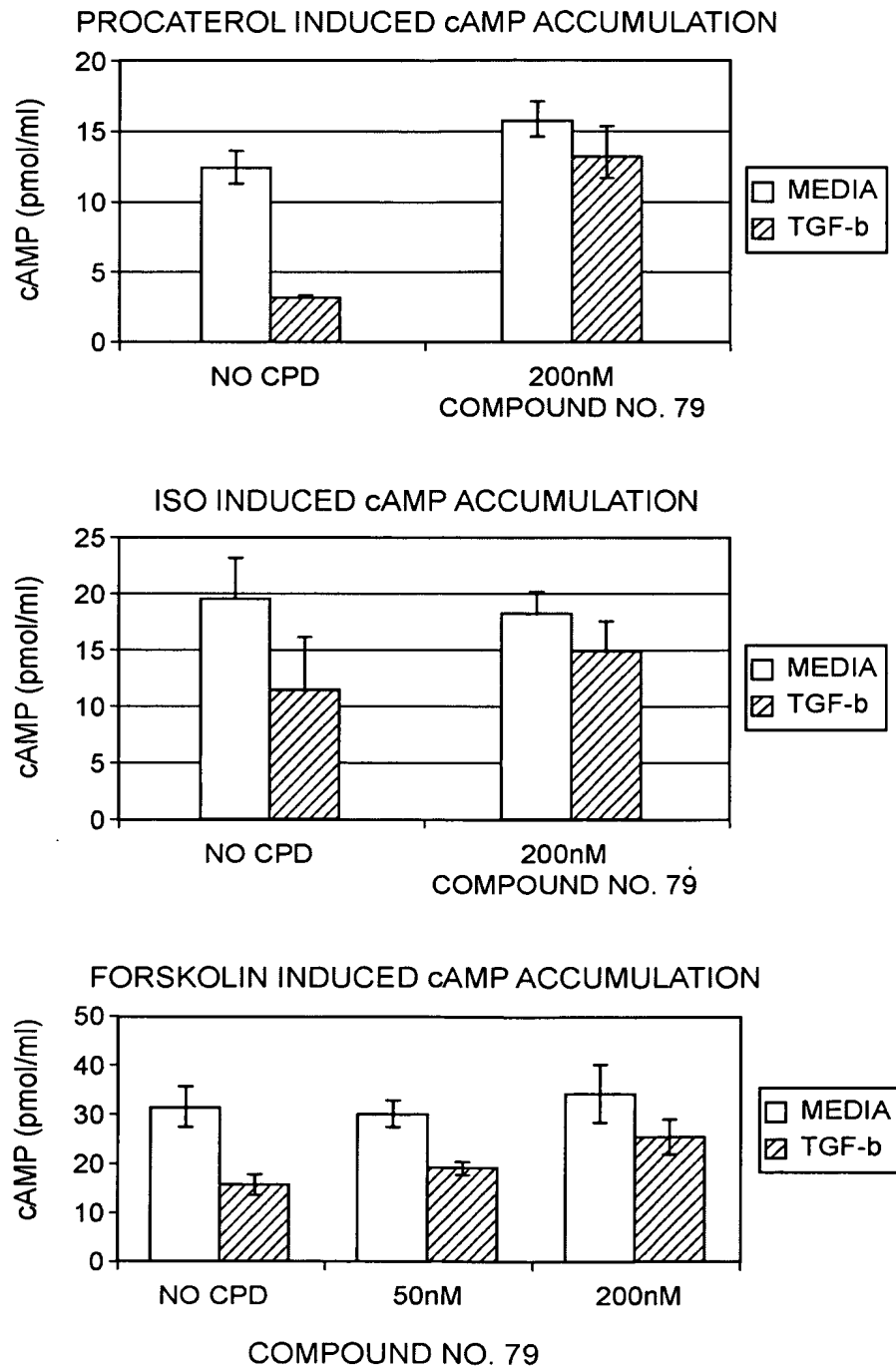
TGF β INDUCES Smad2 PHOSPHORYLATION AND CAUSES
LOSS OF β 2-AR RESPONSE IN RAT CARDIOMYOCYTES



9/28

FIG. 9

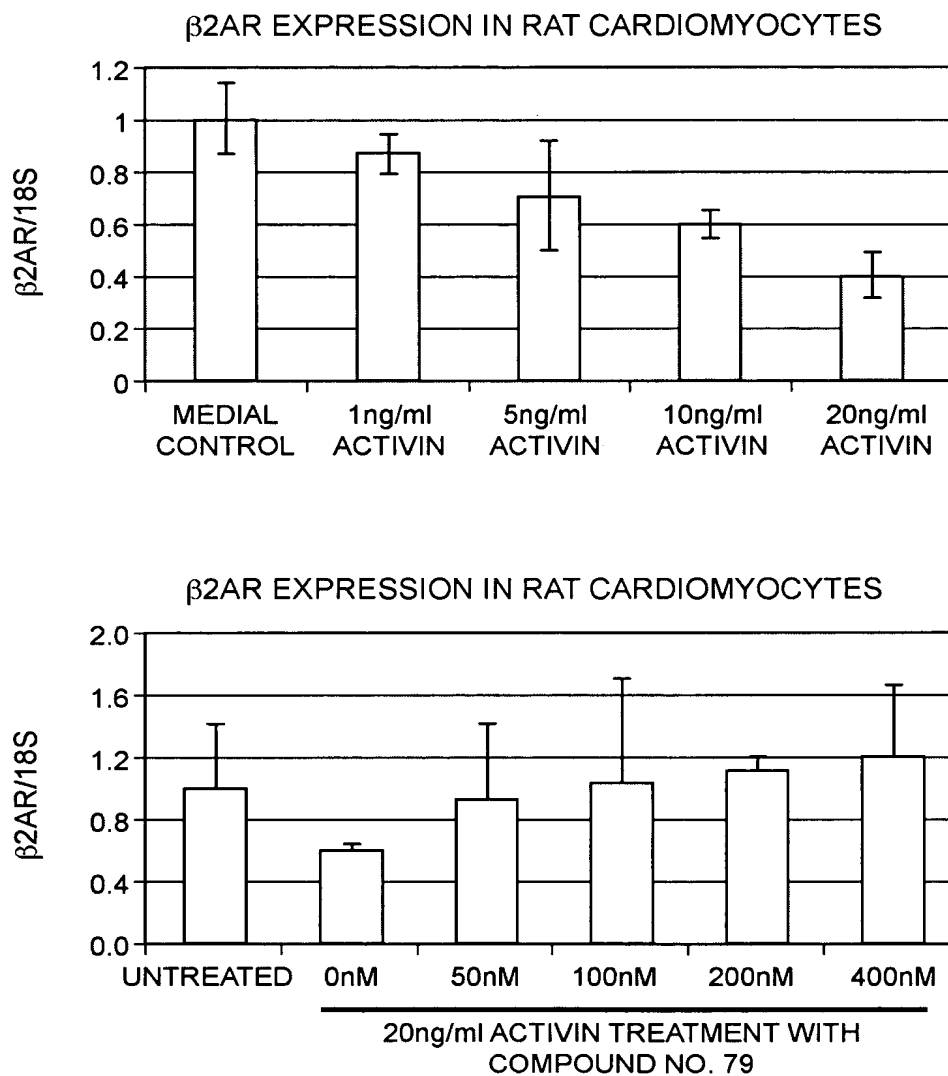
COMPOUND NO. 79 PREVENTS TGF β -INDUCED LOSS OF β 2-AR
RESPONSE/AC ACTIVITY IN RAT NEONATAL CARDIOMYOCYTES



10/28

FIG. 10

ACTIVIN REDUCES β 2-AR mRNA IN RAT NEONATAL
CARDIOMYOCYTES

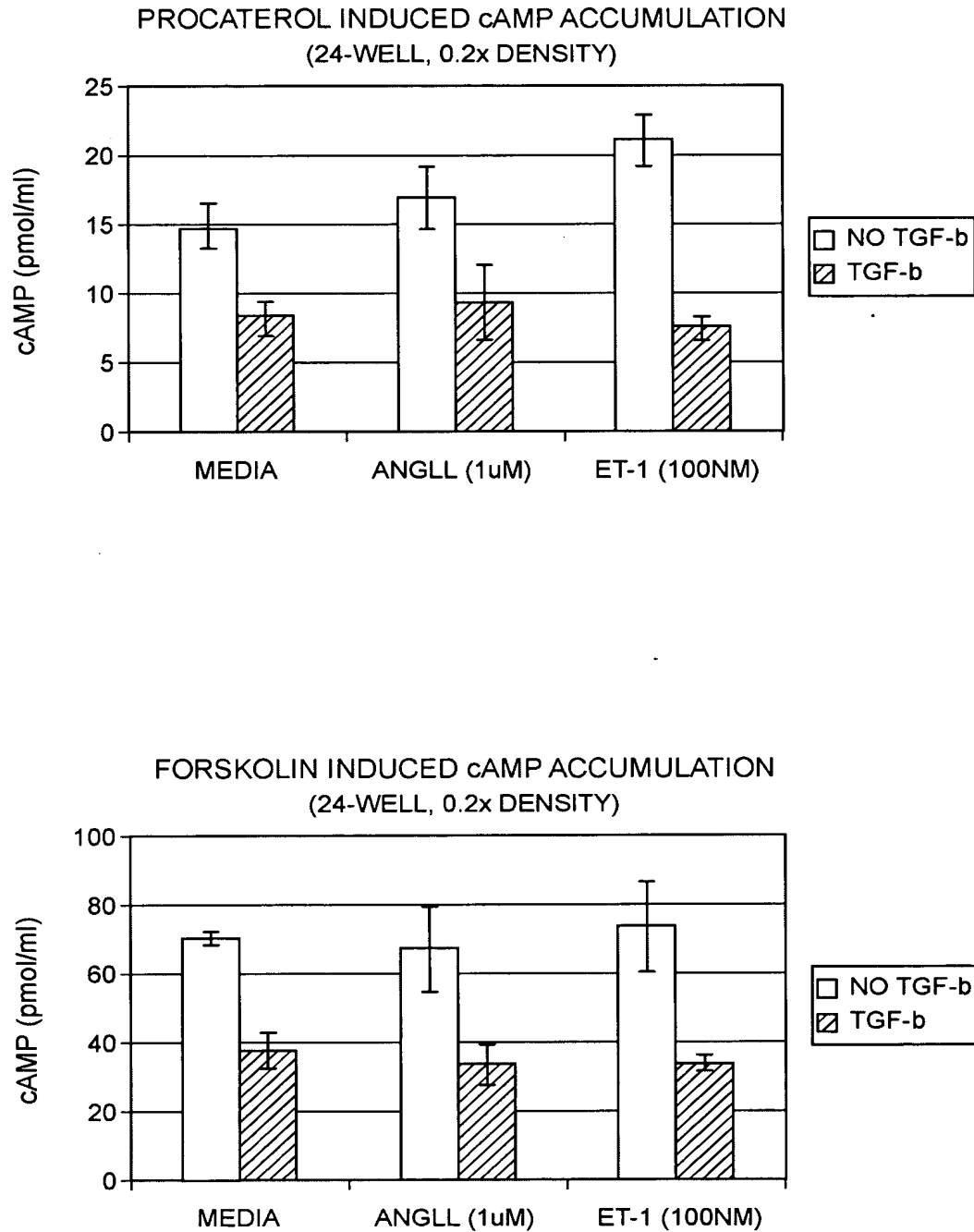


* TAQMAN ANALYSIS SHOWED NO EFFECT ON β 1AR mRNA

11/28

FIG. 11

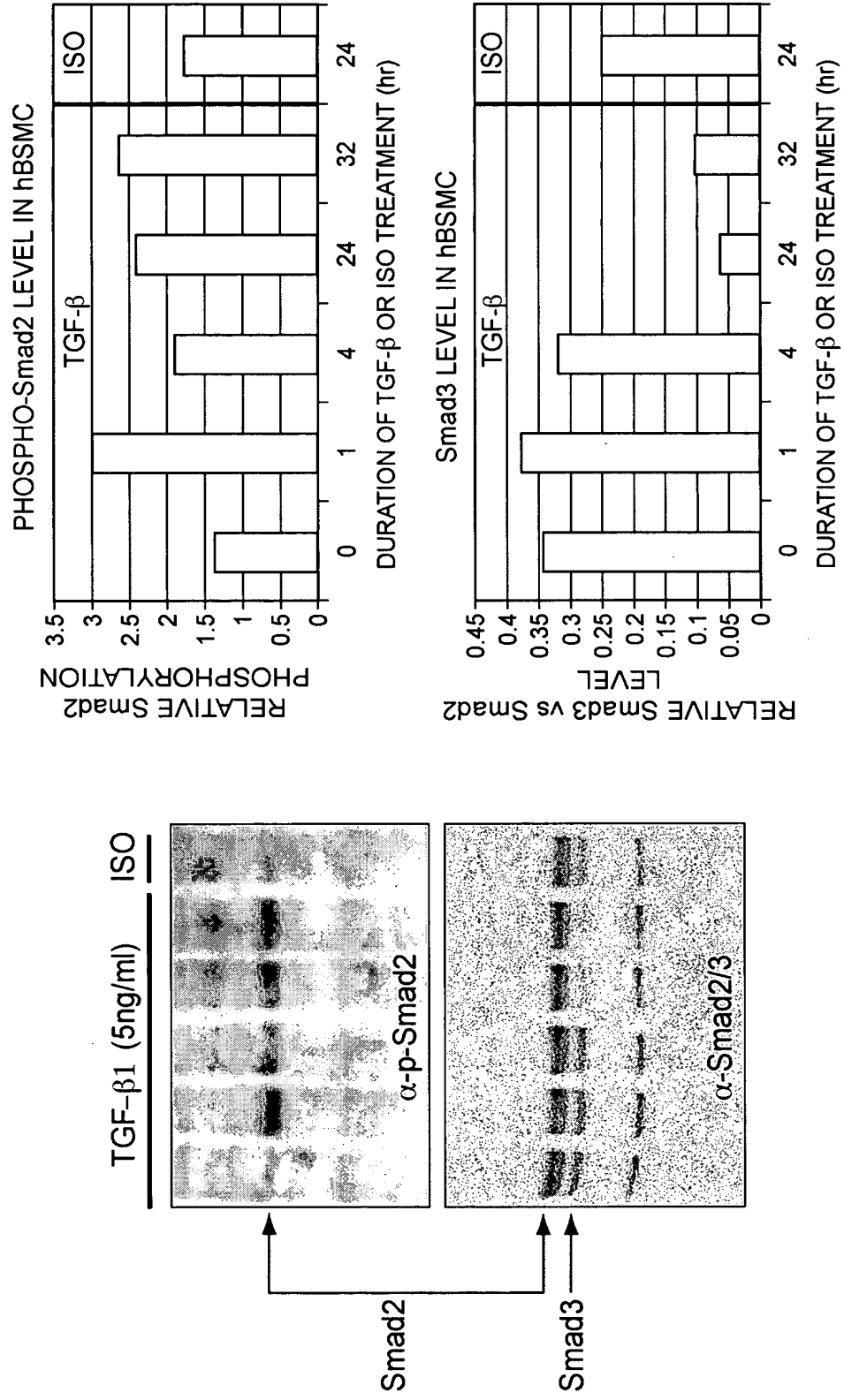
EFFECTS OF TGF β AND HYPERTROPHIC STIMULI
ON β 2-AR SIGNALING IN RAT CARDIOMYOCYTES



+

12/28

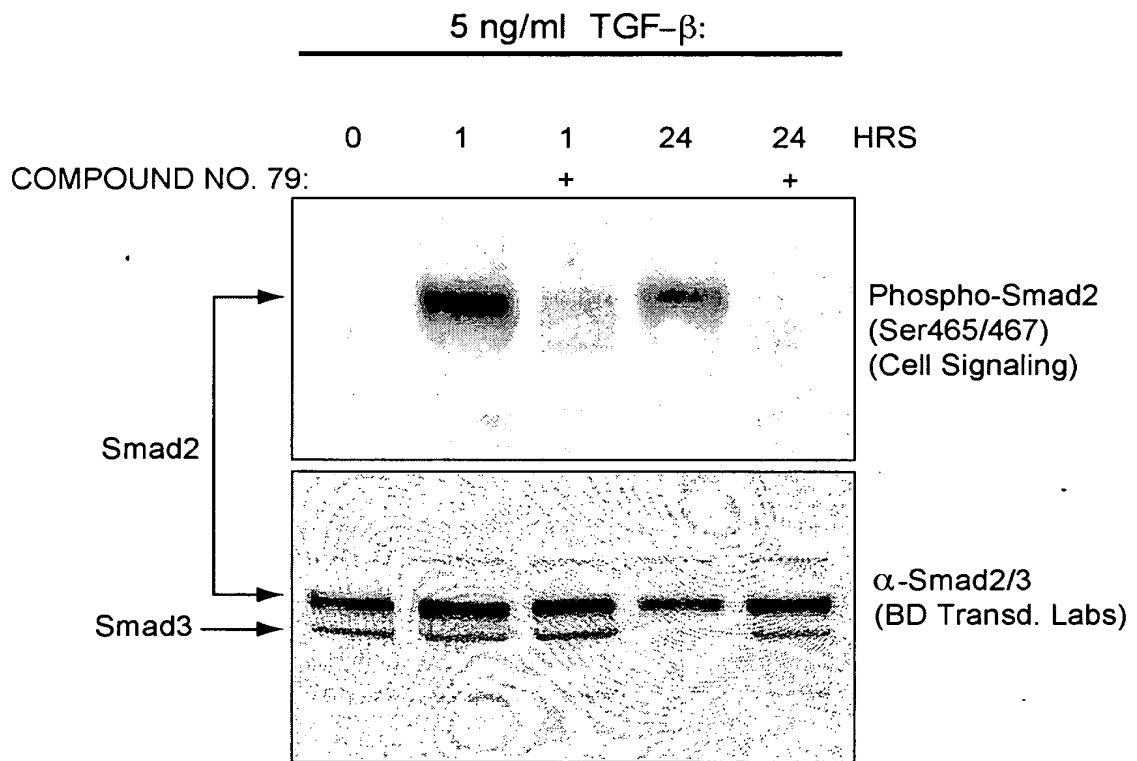
FIG. 12

TGF β INDUCES Smad2 PHOSPHORYLATION AND DOWN-REGULATES Smad3 EXPRESSION IN hBSCC

+

FIG. 13

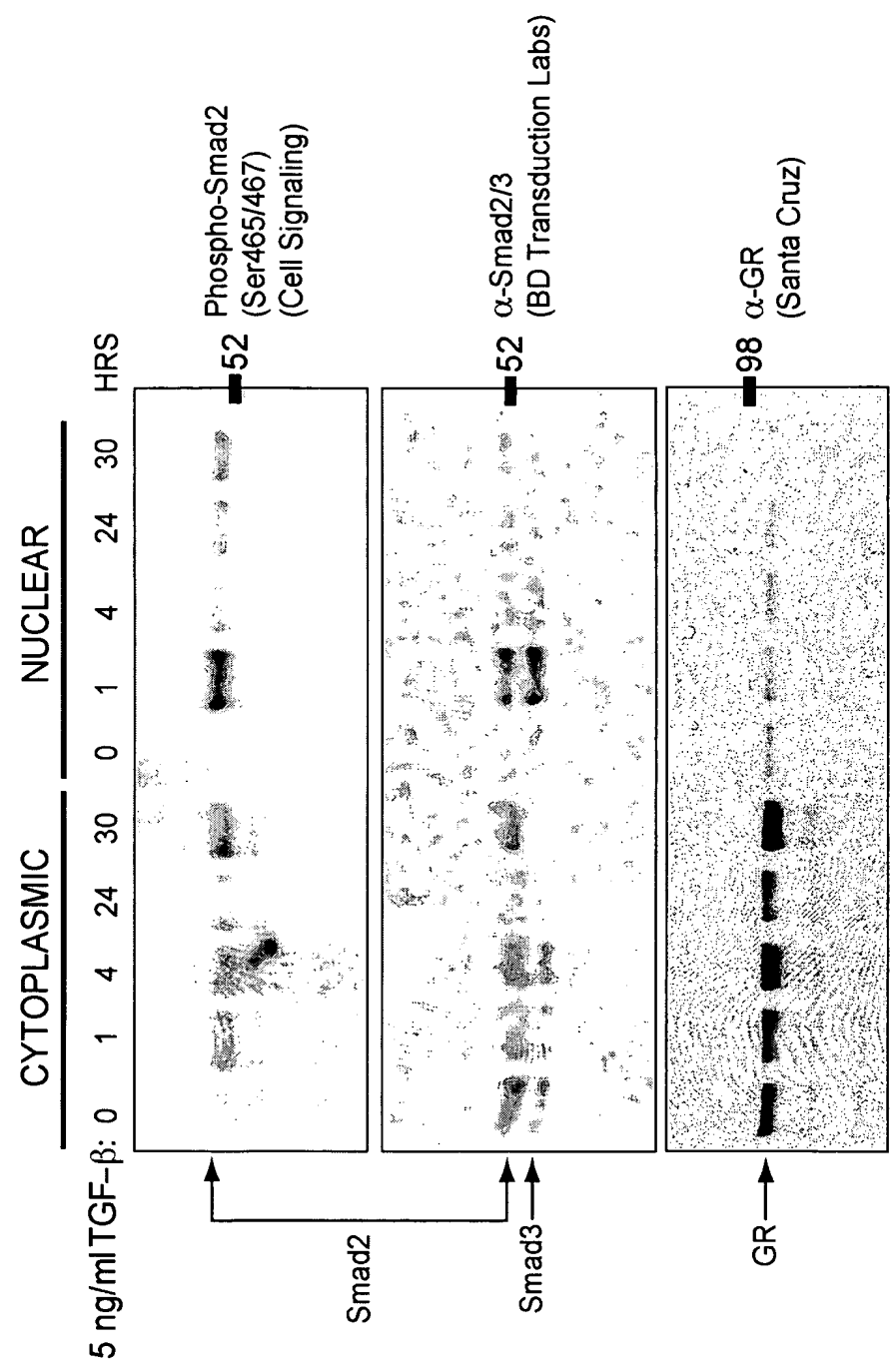
COMPOUND NO. 79 BLOCKS TGF β INDUCED Smad2
PHOSPHORYLATION AND Smad3 DOWN-REGULATION IN hBSMC



+

FIG. 14

TGFβ EXPOSURE INDUCES Smad2/3 TRANSIENT TRANSLOCATION INTO NUCLEUS IN hBSCC



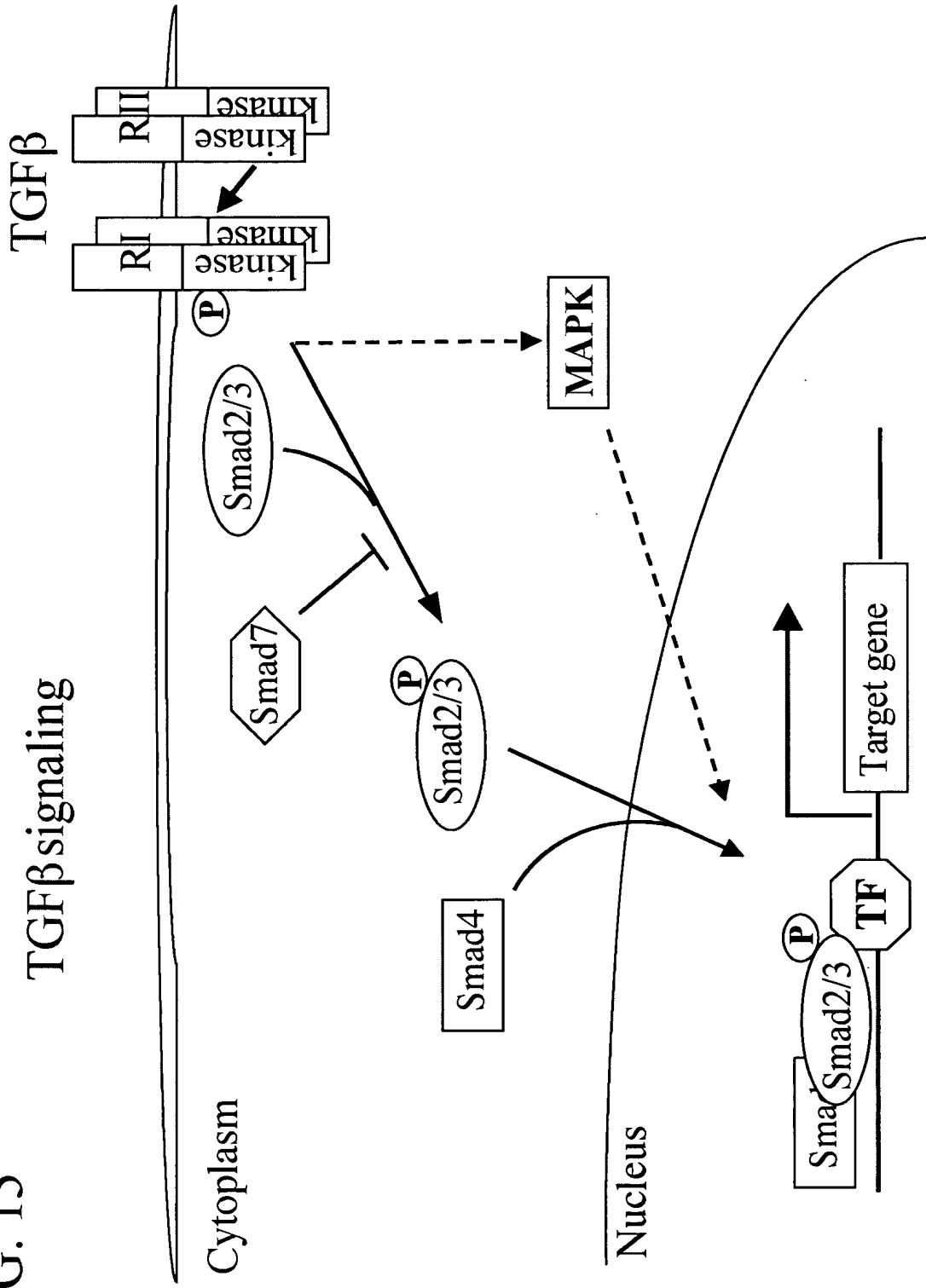
- Glucocorticoid receptor (GR) is cytoplasmic steroid receptor translocating into nucleus in response to hormone stimulation

+

+

FIG. 15

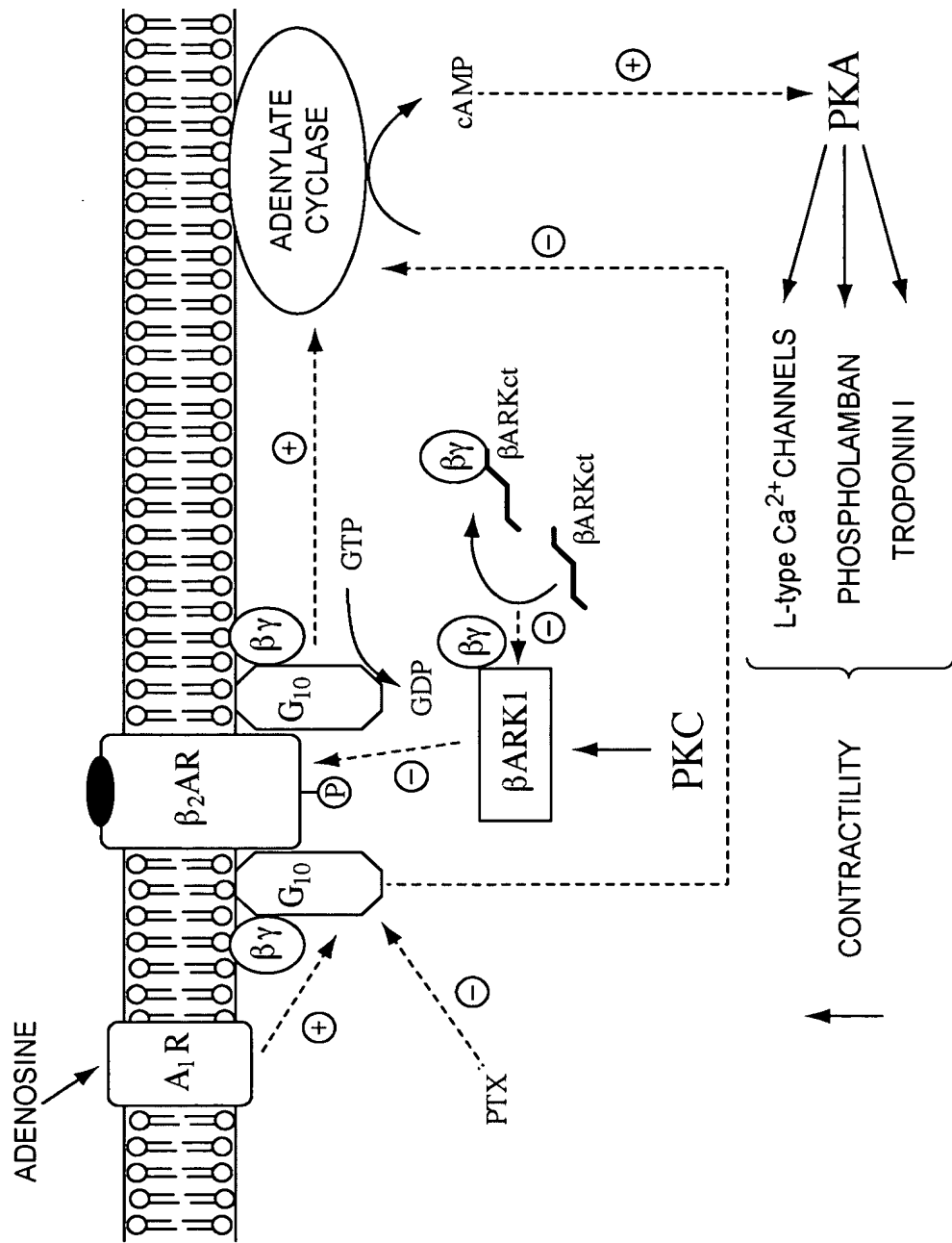
TGF β signaling



+

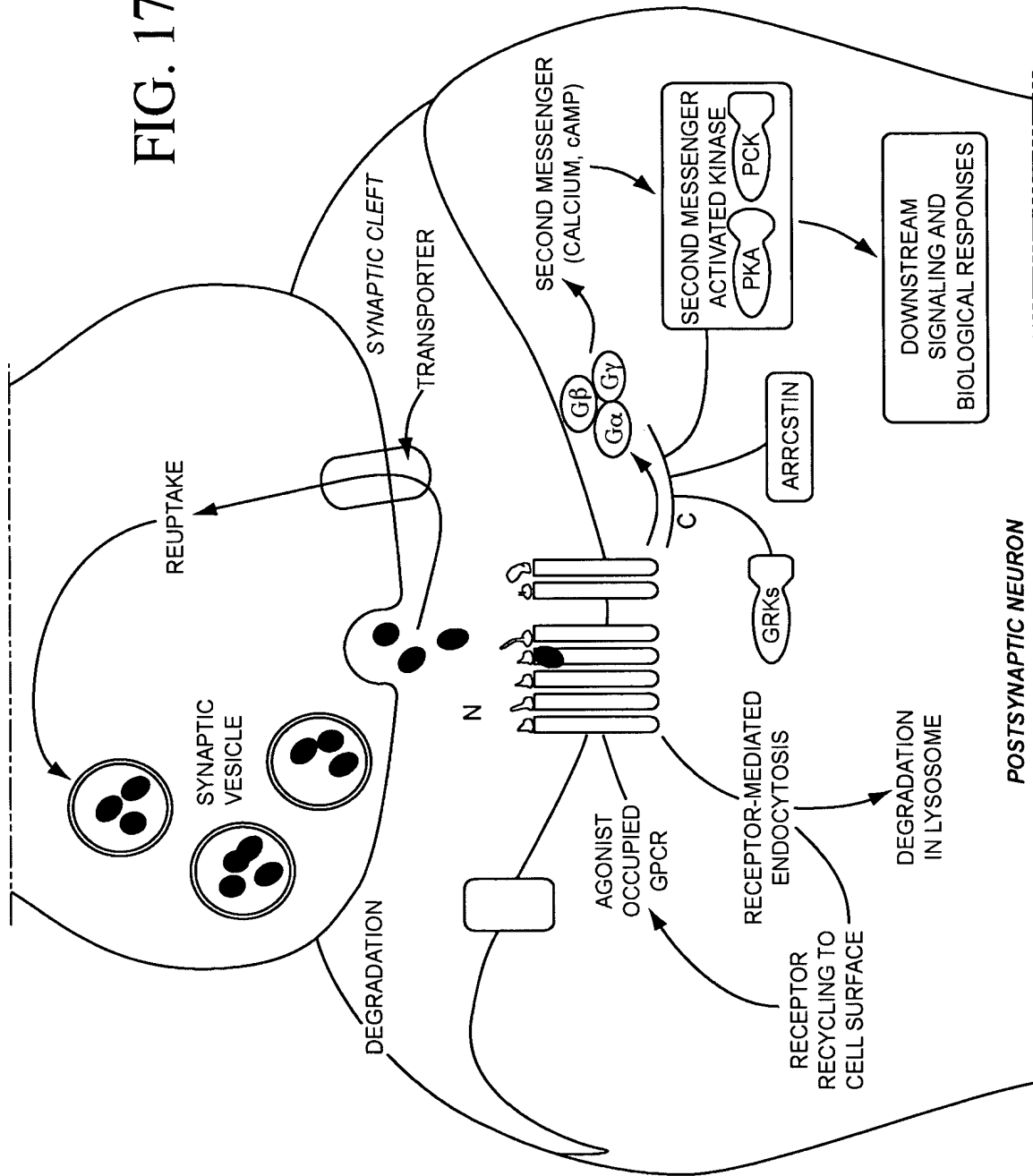
FIG. 16

THE β -ADRENERGIC SIGNALING CASCADE



+

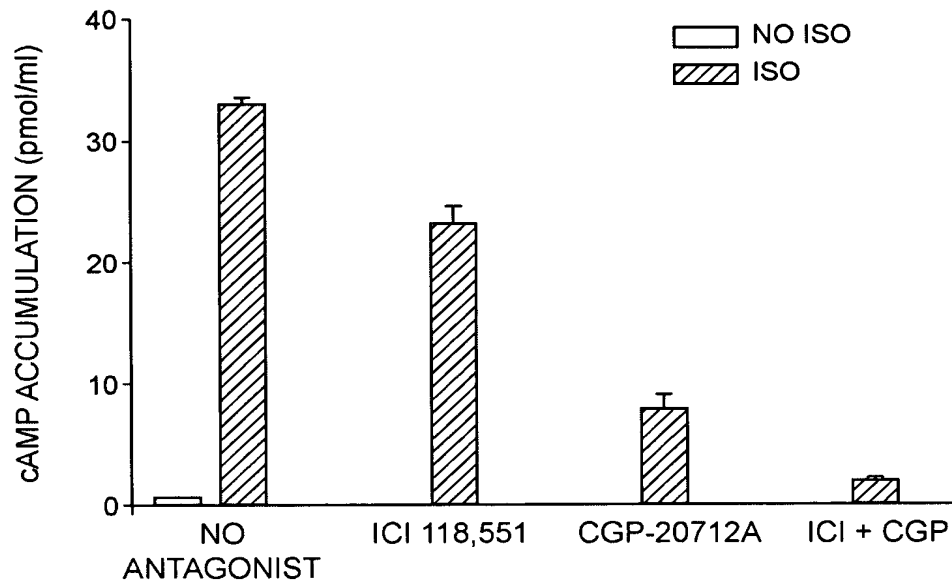
FIG. 17



+

18/28

FIG. 18



19/28

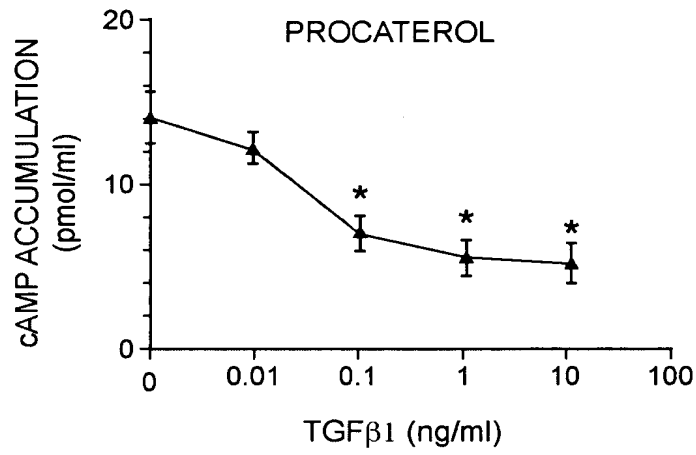


FIG. 19A

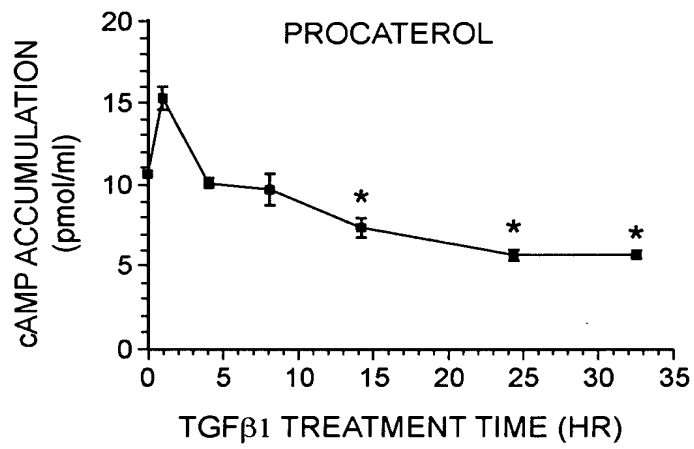


FIG. 19B

20/28

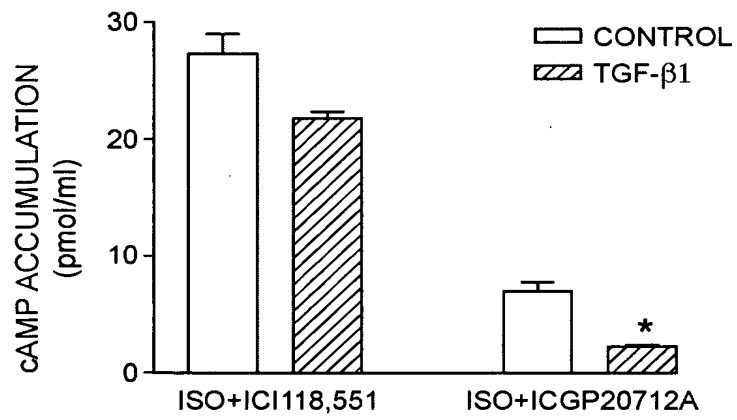


FIG. 19C

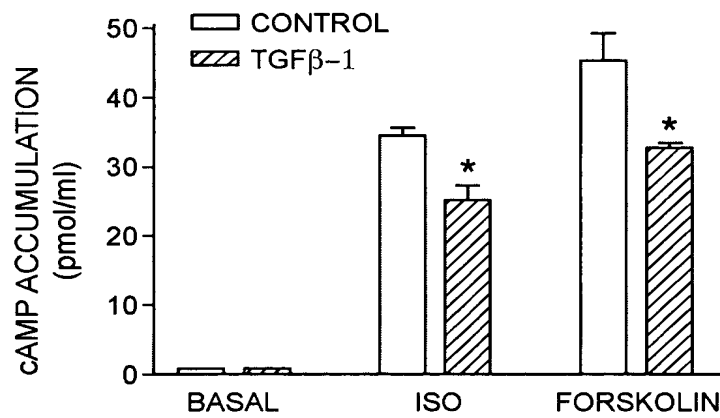


FIG. 19D

21/28

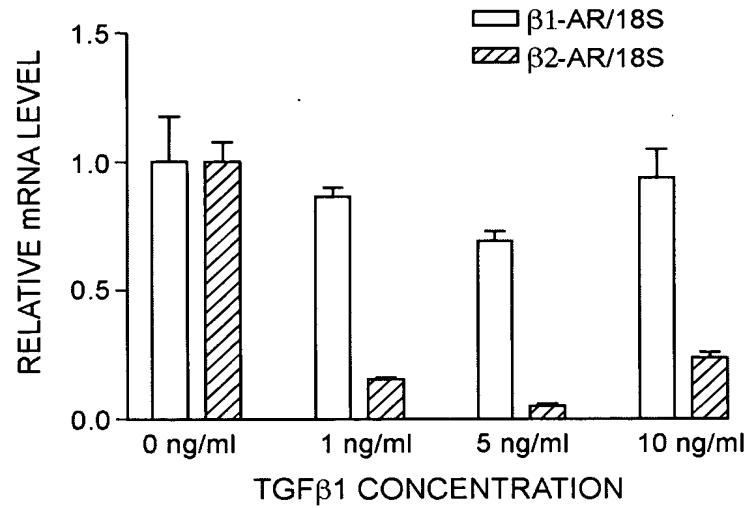


FIG. 20A

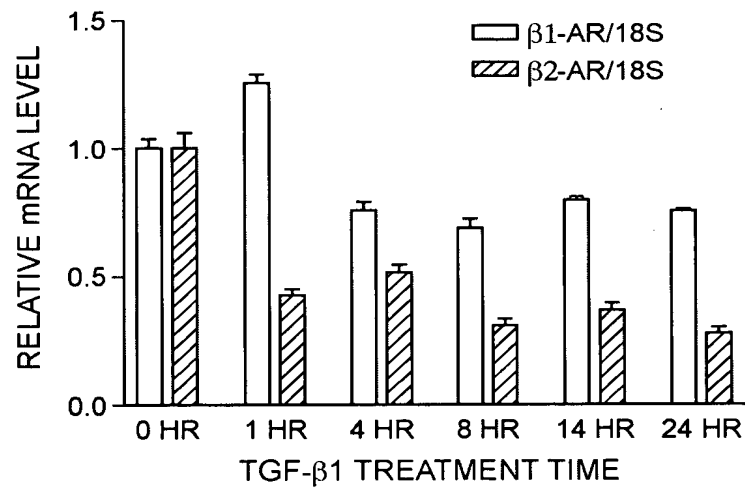


FIG. 20B

22/28

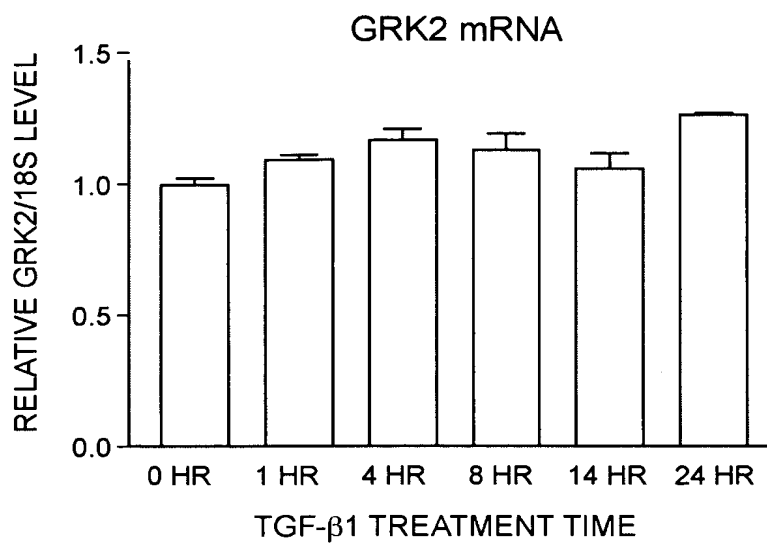


FIG. 21A

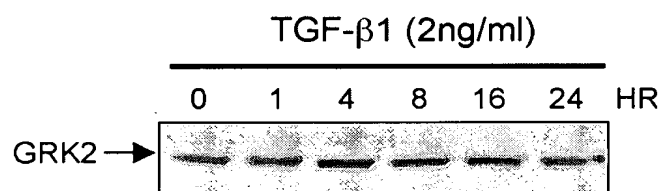


FIG. 21B

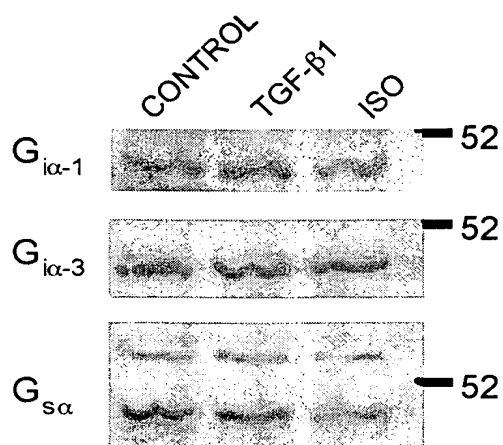


FIG. 21C

23/28

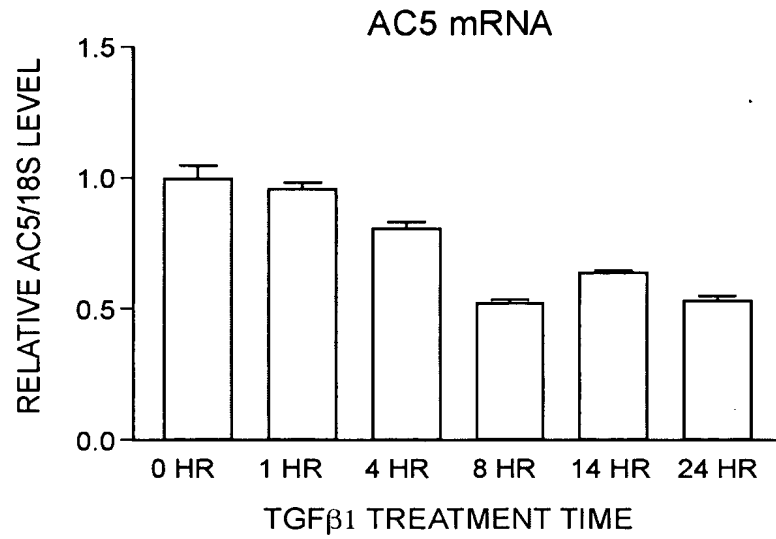


FIG. 21D

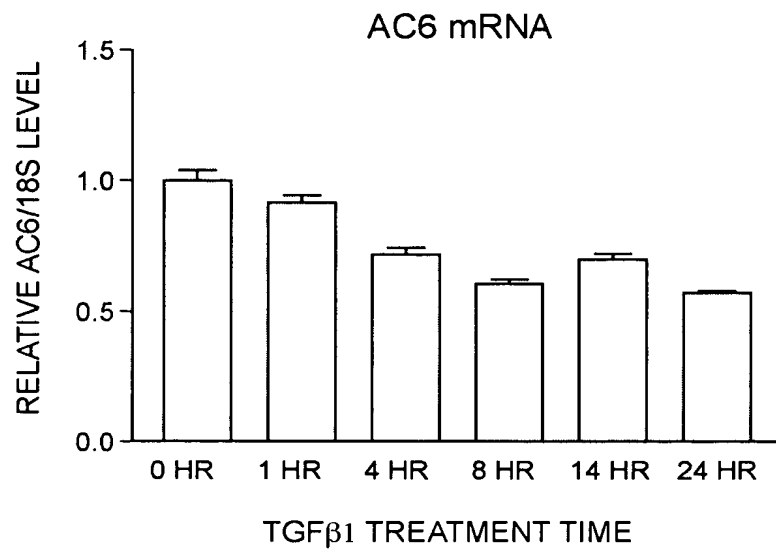


FIG. 21E

24/28

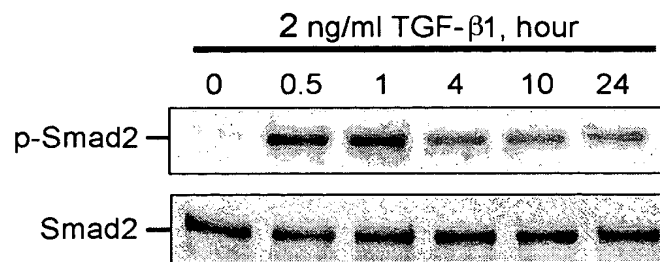


FIG. 22A

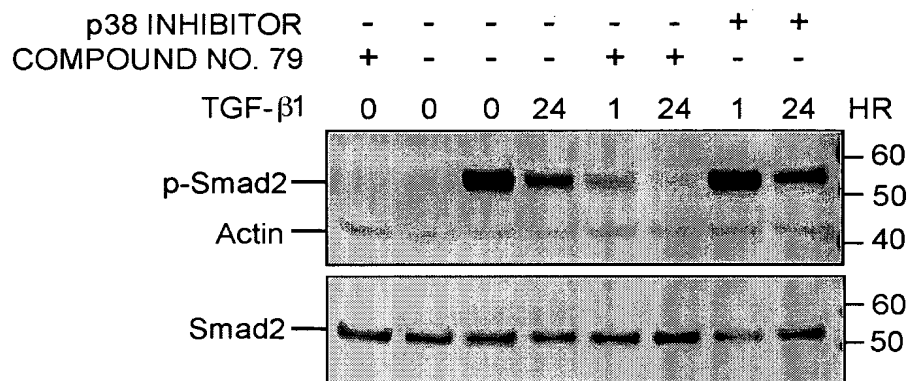


FIG. 22B

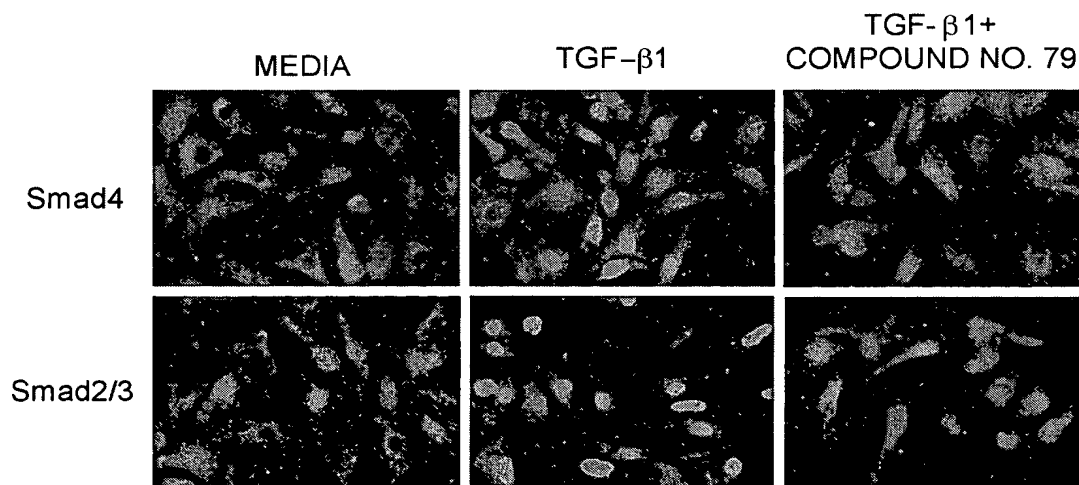


FIG. 22C

25/28

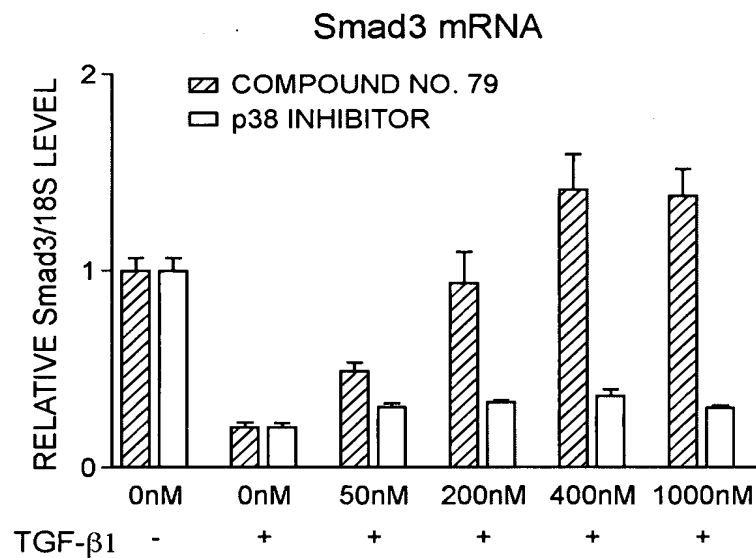


FIG. 23A

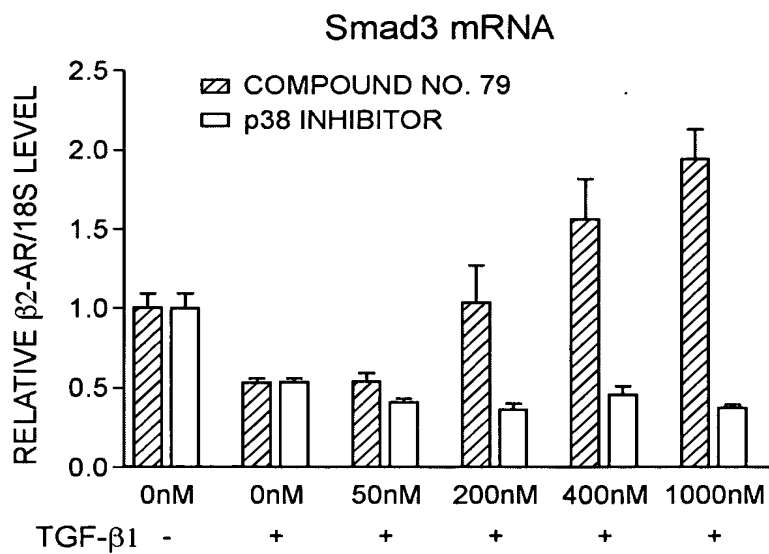


FIG. 23B

26/28

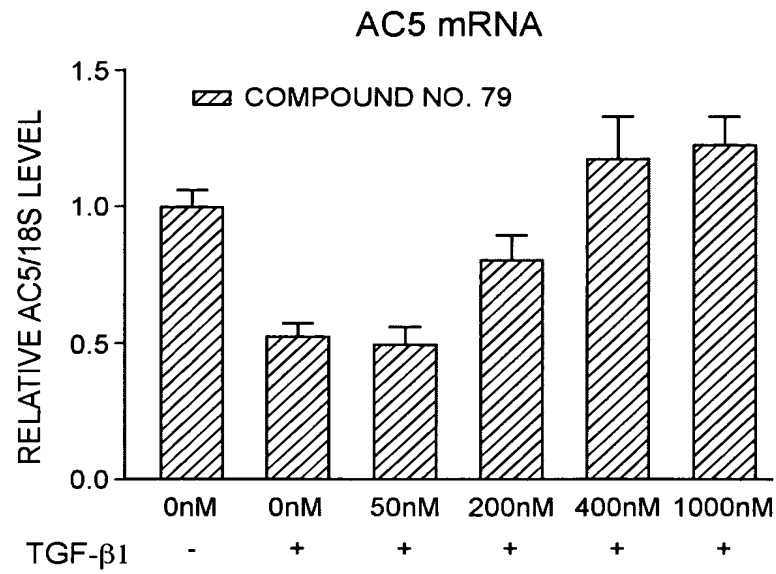


FIG. 23C

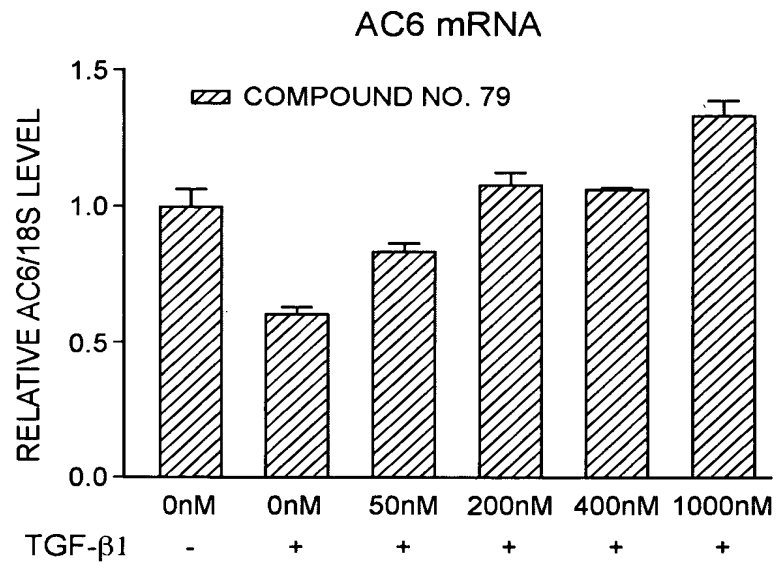


FIG. 23D

27/28

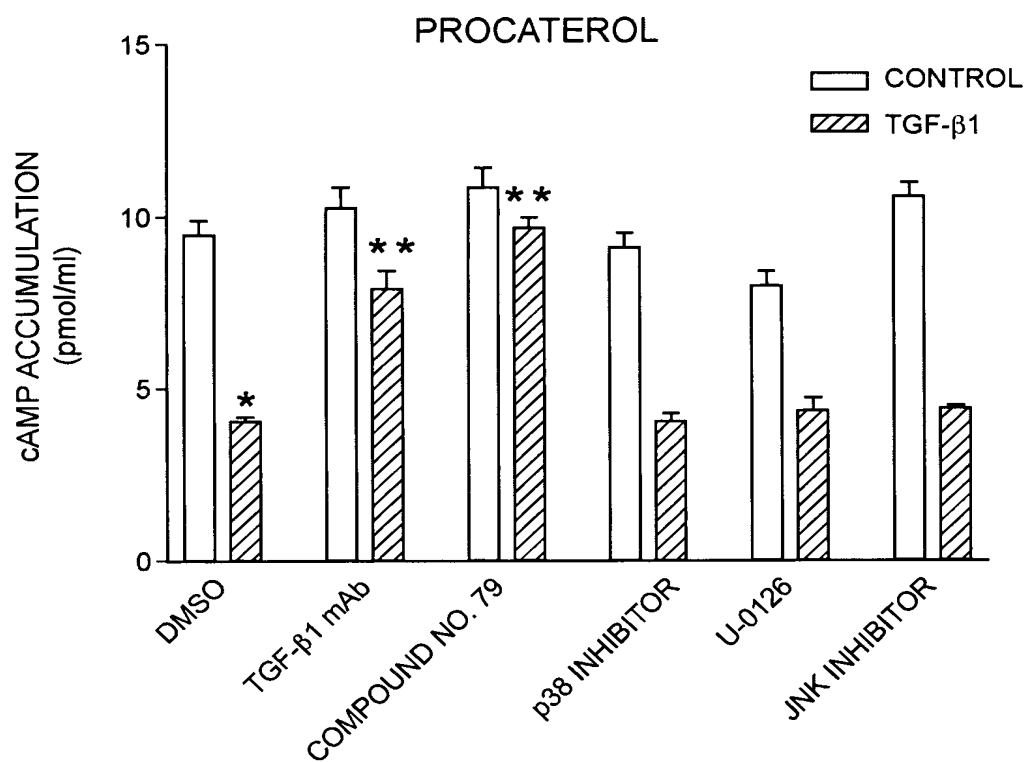


FIG. 24A

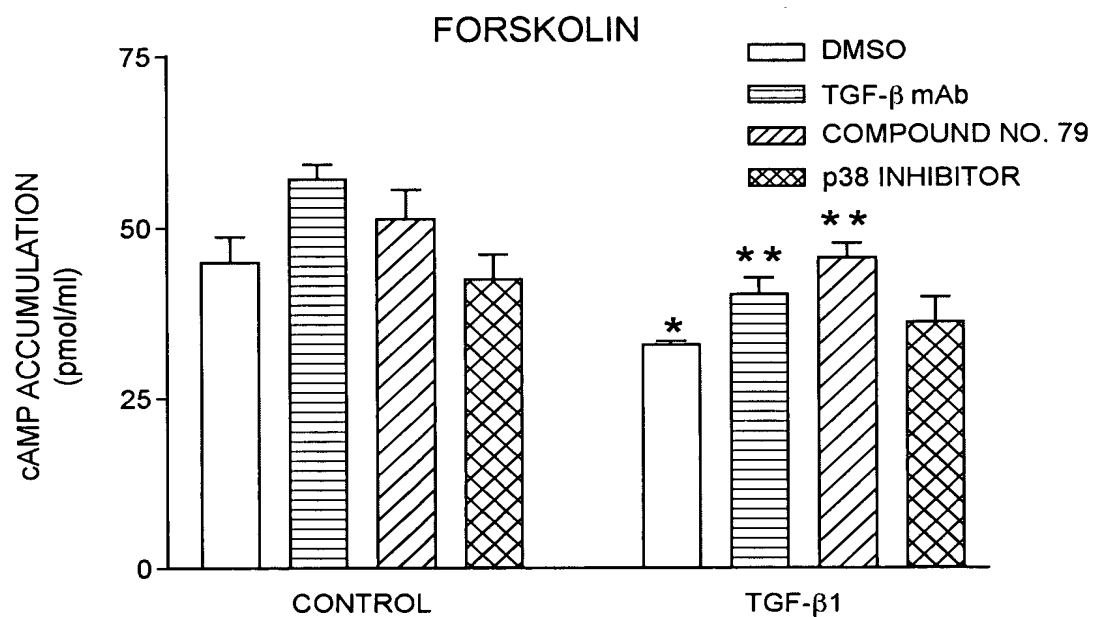
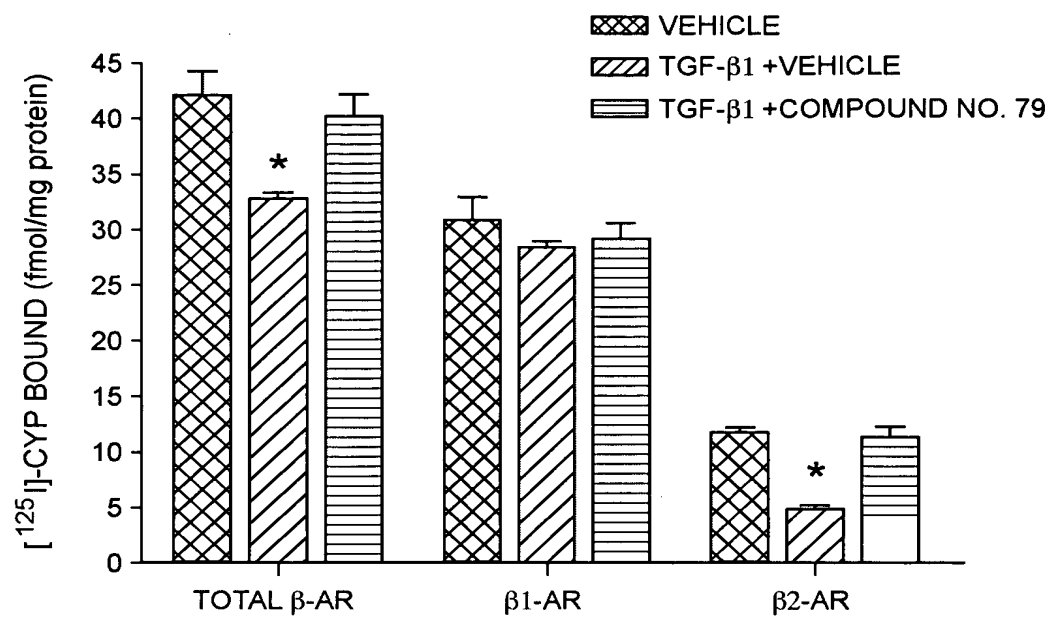


FIG. 24B

**FIG. 25**

ALTERATION OF β -AR BINDING SITES BY TGF- β 1
AND COMPOUND NO. 79 IN CARDIOMYOCYTES